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DOCUMENT-IDENTIFIER: US 6063637 A
TITLE: Sensors for sugars and other metal binding analytes

ABPR:
Sensors (20, 50, 70) for use in detecting the presence of sugars and other analytes (target molecules). The sensor is composed of a metal complex that binds to the target molecule and releases a proton or includes an exchangable ligand which is exchanged for the target molecule during the binding interaction between the metal complex and the target molecule. The result of the binding interaction is the release of a proton, hydroxide ion or ligand species generated during the ligand exchange. Measurement of the release of proton, hydroxide ion or other ligand species from the sensor (20, 50, 70) provides an indirect indication of target molecule concentration. The metal complexes may be attached to support structures (10, 12) to provide both anchoring and positioning of the metal ions to increase selectivity of sugar/metal complex interactions. Detection systems in which pH is used as an indication of proton or hydroxide release are disclosed, as are detection systems in which Cl.sup.- release is used. Methods for monitoring the concentrations of sugars and related molecules using the metal based sensors (20, 50, 70) are also disclosed.

BSPR:
This invention relates generally to devices and methods used to test for and monitor the concentrations in solutions of sugars, amino acids and other compounds capable of complexing metal ions. More particularly, the present invention is directed to sensors which rely on metal coordination/chelation interactions between nucleophilic groups on targeted compounds and the release of protons, hydroxide ions or detectable ligands from metal ion complexes to provide detection and/or measurement of analyte compounds in aqueous, mixed aqueous-organic or organic solutions.

BSPR:
Existing glucose sensing technologies exploit the ability of certain enzymes to selectively recognize glucose and catalyze a chemical reaction (Pickup, J. Trends in Biotechnology, 11, 285-291, (1993)). Many, for example, recruit glucose oxidase to catalyze the oxidation of glucose to gluconic acid and hydrogen peroxide, with electrochemical measurement of the latter. Potentiometric monitoring of gluconic acid production using a pH electrode or a field effect transistor (FET) is also possible. The enzyme-based sensors are simple to use and have relatively high sensing selectivity. They are widely used for one-time measurement of blood-glucose concentrations ex vivo. However, the enzyme system also has numerous disadvantages. These problems include high cost, difficulty in manufacturing, stability, both in ex vivo and in in vivo implantable devices (Alva et al. "Glucose-Oxidase Immobilized Electrode for Potentiometric

Estimation of Glucose," Biosensors and Bioelectronics 6, 663-668, (1991); Shulga et al. "An Alternative Microbiosensor for Hydrogen-Peroxide Based on an Enzyme Field-Effect Transistor with a Fast-Response," Analytica Chimica ACTA 296, 163-170, (1994)). Also, the enzymes cause immunological responses and are difficult to sterilize for long term, continuous, real time measurement of glucose concentrations in vivo (Kerner et al. W., Kiwit, M., Linke, B., Keck, F. S., Zier, H. and Pfeiffer, E. F. "The Function of a Hydrogen Peroxide-Detecting Electroenzymatic Glucose Electrode is Markedly Impaired in Human Sub-cutaneous Tissue and Plasma," Biosensors and Bioelectronics 8, 473-482, (1993)). There is a need to develop sensitive and miniaturizable glucose monitoring devices which will make alternative methods of sample collection, such as from subcutaneous tissue fluid, more feasible for use at home by patients. The development of non-enzymatic approaches to glucose sensing is necessary in order to provide more effective management of diabetes, both for spot monitoring of glucose concentrations as well as for in vivo continuous monitoring.

BSPR:
Another aspect of the present invention is based on the discovery that certain metal complexes which contain substitutable or exchangeable ligands may be used in a method for making soluble and polymeric metal complexing materials suitable for measuring the concentrations of various analytes in solution. These materials are capable of generating protons, hydroxide ions and/or releasing detectable ligands when ligands in the metal complexes are exchanged with targeted analytes. By monitoring the pH changes of the solution or release of detectable ligands, the concentration of the analytes can be determined. Metal complexes with exchangeable ligands can be tailored so that only certain compounds, with both the right metal binding groups and the right binding strength, can cause the release of protons, hydroxide ions or other ligands upon binding to the metals. The analytes that can be targeted by this approach include sugars, aminosugars, polyols, amino acids, amino alcohols, .alpha.-hydroxyl carboxylic acids, ions such as carbonate, phosphate and sulfate, and gaseous species, such as CO and NO, that have the ability to undergo ligand substitution on the metal complexes. In combination with various methods for measuring pH changes or the detectable ligand concentrations, these metal complexing materials can be used for chemical sensing and monitoring applications.

BSPR:
As a further feature of the present invention, a target molecule detection system is provided in which a signal transduction system is used to detect the protons, hydroxide ions or other easily detected ligand species which are released from the sensor metal complexes as a result of ligand exchange with the target molecule. Although any number of detection devices may be used to transduce the signal from the released ligand into an electrical or optical signal, it was found that detection systems based on changes in the solution pH caused by the proton or hydroxide ion release provided many advantages. Proton or hydroxide ion release can be detected simply and accurately by measuring changes in the pH of the solution exposed to the sensor material or other pH-sensitive properties. Alternatively, the solution may be titrated with acid base or after exposure to the sensor to maintain a constant pH. The concentration of target molecule can be determined from the pH change or the amount of acid or base required to maintain the pH.